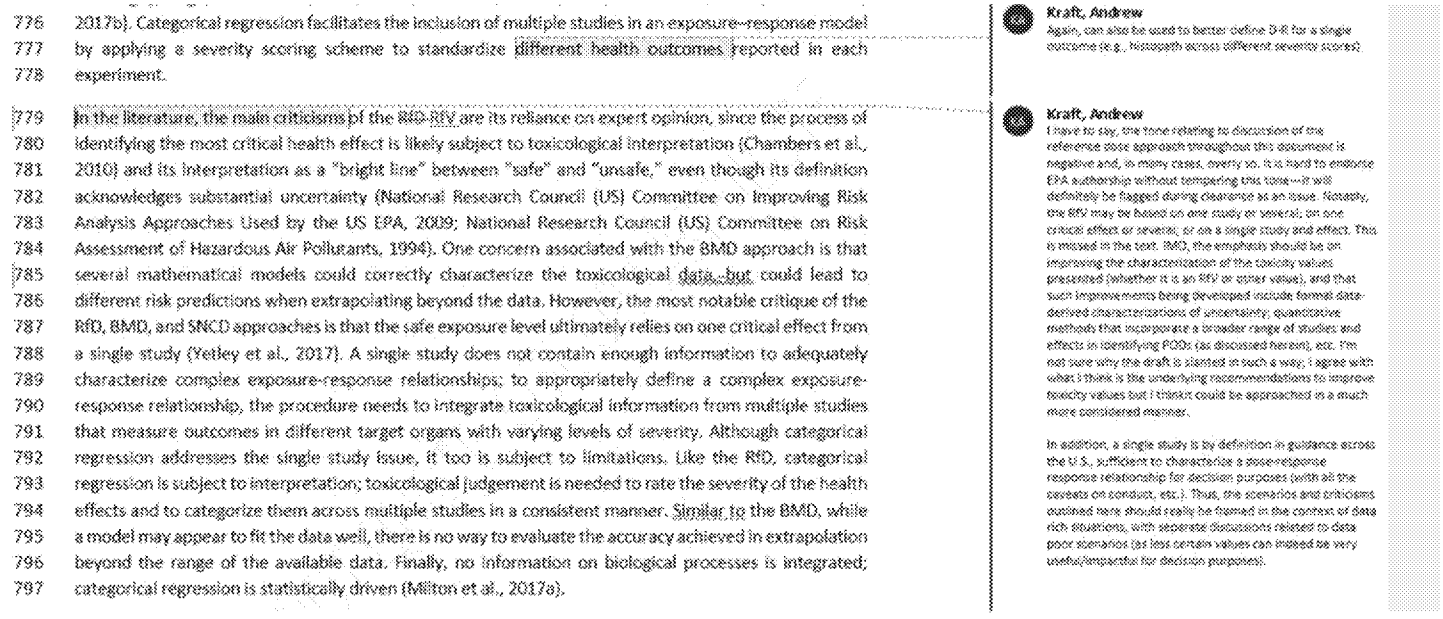
Message

From: Thayer, Kris [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=3CE4AE3F107749C6815F243260DF98C3-THAYER, KRI]
Sent: 2/17/2020 12:49:01 AM
To: Daniel Krewski [dkrewski@uottawa.ca]
Subject: RE: MS1 Krewski et al Workshop Report_200130
Attachments: MS1 Krewski et al Workshop Report_200130_ak_kat.docx

Here you go Dan, sorry again for the delay.

Andrew did a pass for any major issues. I think most of his comments are pretty easy to address but this paragraph raised some potential clearance issues….



776 2017b). Categorical regression facilitates the inclusion of multiple studies in an exposure–response model
777 by applying a severity scoring scheme to standardize different health outcomes reported in each
778 experiment.

779 In the literature, the main criticisms of the BMD-RfV are its reliance on expert opinion, since the process of
780 identifying the most critical health effect is likely subject to toxicological interpretation (Chambers et al.,
781 2010) and its interpretation as a "bright line" between "safe" and "unsafe," even though its definition
782 acknowledges substantial uncertainty (National Research Council (US) Committee on Improving Risk
783 Analysis Approaches Used by the US EPA, 2009; National Research Council (US) Committee on Risk
784 Assessment of Hazardous Air Pollutants, 1994). One concern associated with the BMD approach is that
785 several mathematical models could correctly characterize the toxicological data, but could lead to
786 different risk predictions when extrapolating beyond the data. However, the most notable critique of the
787 RfD, BMD, and SNCD approaches is that the safe exposure level ultimately relies on one critical effect from
788 a single study (Yetley et al., 2017). A single study does not contain enough information to adequately
789 characterize complex exposure-response relationships; to appropriately define a complex exposure-
790 response relationship, the procedure needs to integrate toxicological information from multiple studies
791 that measure outcomes in different target organs with varying levels of severity. Although categorical
792 regression addresses the single study issue, it too is subject to limitations. Like the RfD, categorical
793 regression is subject to interpretation; toxicological judgement is needed to rate the severity of the health
794 effects and to categorize them across multiple studies in a consistent manner. Similar to the BMD, while
795 a model may appear to fit the data well, there is no way to evaluate the accuracy achieved in extrapolation
796 beyond the range of the available data. Finally, no information on biological processes is integrated;
797 categorical regression is statistically driven (Milton et al., 2017a).

Kraft, Andrew
Again, can also be used to better define BMR for a single outcome (e.g., histopath across different severity scores).

Kraft, Andrew
I have to say, the tone relating to discussion of the reference dose approach throughout this document is negative and, in many cases, overly so. It is hard to endorse EPA authorship without tempering this tone—it will definitely be flagged during clearance as an issue. Notably, the RfV may be based on one study or several, on one critical effect or several, or on a single study and effect. This is missed in the text. IMO, the emphasis should be on improving the characterization of the toxicity values presented (whether it is an RfV or other value), and that such improvements being developed include formal data-derived characterizations of uncertainty; quantitative methods that incorporate a broader range of studies and effects in identifying PODs (as discussed herein), etc. I'm not sure why the draft is slanted in such a way. I agree with what I think is the underlying recommendations to improve toxicity values but I think it could be approached in a much more considered manner.

In addition, a single study is by definition in guidance across the U.S., sufficient to characterize a dose-response/response relationship for decision purposes (with all the caveats on conduct, etc.). Thus, the scenarios and criticisms outlined here should really be framed in the context of data rich situations, with separate discussions related to data poor scenarios (as less certain values can instead be very useful/impactful for decision purposes).

From: Daniel Krewski <dkrewski@uottawa.ca>
Sent: Wednesday, February 12, 2020 1:39 PM
To: Thayer, Kris <thayer.kris@epa.gov>
Subject: RE: MS1 Krewski et al Workshop Report_200130

Monday OK Kris – if you can give us a go-ahead to submit on Monday, that would be ideal (even if further review by EPA is needed).

Please keep in mind we can still make further adjustments during the course of the review process with ALTEX.

Thanks for your continued support and input . . . once we get Workshop #1 Proceedings submitted, I'd like to call the Steering Committee together to discuss the preparing of proceedings of Workshop #2 and begin planning Workshop #3, where we pull it all together with the case studies.

With best regards.

Dan K.

From: Thayer, Kris [mailto:thayer.kris@epa.gov]
Sent: February 12, 2020 6:40 AM

To: Daniel Krewski <dkrewski@uottawa.ca>
Subject: RE: MS1 Krewski et al Workshop Report_200130

Attention : courriel externe | external email
Dan – actually can you give us until Monday to do a fast show-stopper review?

From: Daniel Krewski <dkrewski@uottawa.ca>
Sent: Thursday, January 30, 2020 9:33 PM
To: Thayer, Kris <thayer.kris@epa.gov>
Subject: MS1 Krewski et al Workshop Report_200130

Kris, just a note to let you know that all seven manuscripts comprising the proceedings of the December 2018 Workshop at uOttawa are now in final form and ready for submission to ALTEX. (Although each paper will be submitted by the designated corresponding author, ALTEX would like all seven papers to be submitted at about the same time.)

Health Canada has completed its internal review, and their (comparatively minor, but helpful) comments have been addressed.

At this point, in order to move the proceedings forward, I'm wondering if I may proceed with submission of the main workshop report (attached), with the EPA review to be done in parallel with the ALTEX review?

I would like to get this submitted as soon as possible, and focus on the preparation of the proceedings of the December 2019 Workshop, and planning for the third and final workshop in December, 2020.

With best wishes for the New Year.

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